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# Functional connectivity homogeneity correlates with duration of temporal lobe epilepsy

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ABSTRACT

Temporal lobe epilepsy (TLE) is often associated with progressive changes to seizures, memory, and mood during its clinical course. However, the cerebral changes related to this progression are not well understood. Because the changes may be related to changes in brain networks, we used functional connectivity MRI (fcMRI) to determine whether brain network parameters relate to the duration of TLE. Graph theory-based analysis of the sites of reported regions of TLE abnormality was performed on resting-state fMRI data in 48 subjects: 24 controls, 13 patients with left TLE, and 11 patients with right TLE. Various network parameters were analyzed including betweenness centrality (BC), clustering coefficient (CC), path length (PL), small-world index (SWI), global efficiency (GE), connectivity strength (CS), and connectivity diversity (CD). These were compared for patients with TLE as a group, compared to controls, and for patients with left and right TLE separately. The association of changes in network parameters with epilepsy duration was also evaluated. We found that CC, CS, and CD decreased in subjects with TLE compared to control subjects. Analyzed according to epilepsy duration, patients with TLE showed a progressive reduction in CD. In conclusion, we found that several network parameters decreased in patients with TLE compared to controls, which suggested reduced connectivity in TLE. Reduction in CD associated with epilepsy duration suggests a homogenization of connections over time in TLE, indicating a reduction of the normal repertoire of stronger and weaker connections to other brain regions.

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## 1. Introduction

Although temporal lobe epilepsy (TLE) may be effectively treated by a focal temporal lobe resection, it has been found to have widespread extratemporal involvement in both the ictal and interictal states [1]. This suggests a more widespread network abnormality present across brain regions, which has been identified as extratemporal structural and functional abnormalities using MRI [2], EEG [3], neuropsychology testing [4], functional MRI (fMRI) [5], diffusion tensor imaging (DTI) [6], single-photon emission computed tomography (SPECT), and positron emission tomography (PET) studies [7]. Extension of the disease outside the epileptogenic zone may be contributory to the incomplete control of seizures in up to 30% of patients who undergo surgical treatment of TLE [8] as well as the cognitive and neurobehavioral changes in TLE [9].

Functional connectivity MRI (fcMRI) has identified network-level abnormalities in TLE in the interictal state through various techniques of studying brain networks collectively called "connectomics" [10–13]. Unlike techniques based on pairwise comparisons such as seed-based methods and independent component analysis, graph theory takes into account the full brain network structure by providing a model represented by a collection of nodes and edges and deriving specific network topological properties. This enables the study of individual nodes as well as the network as a whole [14]. The different connectivity techniques examine different aspects of the network structure and have their own particular strengths and limitations. Early encouraging findings suggest that topologic measures by graph theory analysis may improve clinical interpretability [15]. As would be expected, TLE has shown several network changes that help explain the underlying pathophysiology and has been shown to have a clinical utility [16]. Progressive changes in the brain network of patients with TLE have been previously shown using graph analysis of structural MRI, DTI, and EEG [17–19] but have not been explored using fMRI connectivity.

*Abbreviations:* fcMRI, functional connectivity MRI; BC, betweenness centrality; CC, clustering coefficient; PL, path length; SWI, small-world index; GE, global efficiency; CS, connectivity strength; CD, connectivity diversity.

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In this study, we used graph theoretic analysis of fcMRI data in patients with TLE and healthy controls to (1) detect abnormal network parameters in patients with TLE compared to healthy controls, (2) evaluate whether these changes are correlated with the duration of TLE, and (3) evaluate whether such network changes differ with the lateralization of TLE.

## 2. Materials and methods

### 2.1. Subjects

The study population of 48 subjects included 13 with left TLE, 11 with right TLE, and 24 controls (Table 1). Written informed consent was obtained from all subjects prior to scanning in accordance with the guidelines of the University of California, Los Angeles (UCLA) Institutional Review Board. Control subjects had normal structural MRIs, and none had a history of neurologic illness or were taking a neurologic medication. Subjects with epilepsy were recruited from the UCLA Seizure Disorder Center following comprehensive diagnostic testing and subsequent anterior-mesial temporal lobe resective epilepsy surgery. The diagnostic evaluation for all subjects included video-EEG monitoring, high-resolution MRI, FDG-PET scanning, neuropsychological testing, and postoperative examination of the resected tissue.

### 2.2. Imaging and functional connectivity

Functional MRI was performed after the comprehensive epilepsy surgery evaluation and prior to epilepsy surgery. Patients remained on their regular medications during the fMRI. None of the patients had a seizure in the 24 h preceding the imaging. Participants were instructed to relax with eyes closed during imaging. No auditory stimulus was present except for the acoustic noise from imaging. None of the patients had seizures during the study as confirmed by the simultaneous EEG obtained during fMRI. The EEG results were not included in the data analysis other than to exclude seizures. Details of the simultaneous EEG methods have been described previously [20]. Neuroimaging and fMRI preprocessing steps are similar to those described by us previously [5]. Imaging was performed with a 3-T MRI system (Siemens Trio, Erlangen, Germany). Functional imaging was performed with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 210 mm, matrix = 64 × 64, and 34 slices with slice thickness of 4 mm. High-resolution structural images were obtained during the same imaging study with the following parameters: TR = 20 ms, TE = 3 ms, FOV = 256 mm, matrix = 256 × 256, and 160 slices with slice thickness of 1 mm. The images were acquired in the axial plane using a spoiled gradient recalled (SPGR) sequence for the anatomical images and an echo planar imaging (EPI) sequence for the functional images. The imaging sessions included multiple simultaneous EEG and fMRI recordings, each lasting 5 to 15 min. For resting-state fMRI analysis, 20 min of BOLD fMRI data was used for each subject. Average head movement values for the subject groups were as follows: healthy controls, 0.24 mm; patients with left TLE, 0.25 mm; and patients with right TLE, 0.34 mm. Excessive head movement was corrected using "motion scrubbing" [21]. Tissue-type segmentation was performed on each participant's structural image using FAST (FMRIB's Automated Segmentation Tool) [22] before being aligned to their respective BOLD images. White matter signal and cerebrospinal fluid signals were obtained using the segmented masks. The following were included as temporal covariates and regressed out using linear regression: 6 motion parameters, white matter signal, cerebrospinal fluid signal, and their associated derivatives. The residuals were then filtered through a low-pass filter (<0.1 Hz).

**Table 1**
Demographic data of patients with left and right TLE.

| Age | Sex | Handedness | Sz onset age (years) | Sz duration (years) | Sz frequency (per month) | AEDs | MRI | Pathology | SF at last visit | Time since surgery (months) | Neuropsychology memory dysfunction |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Patients with left TLE* | | | | | | | | | | | |
| 40 | M | R | 20 | 20 | 1 | LTG, OXC | Normal | Normal | Yes | 48 | Normal |
| 40 | M | R | 4 | 36 | 3 | LEV, LTG | L MTS | MTS + CD | Yes | 48 | V > NV |
| 35 | F | R | 6 | 29 | 2 | CBZ, LEV, LTG | L MTS | Gliosis | Yes | 31 | Bilateral (L > R) TL dysfunction |
| 23 | F | R | 17 | 6 | 7 | PHT | L MTS | CD | Yes | 45 | V |
| 20 | F | R | 12 | 8 | 7 | VPA, PGB | Normal | CD | Yes | 25 | Normal |
| 27 | F | L | 9 | 18 | 1 | PHT, LTG, LEV | L MTS | CD | Yes | 48 | V |
| 46 | F | L | 1 | 45 | 5 | LTG, LCM | L MTS | CD | Yes | 36 | NV + V |
| 45 | M | L | 40 | 5 | 2 | LEV | L MTS | Normal | Yes | 27 | NV + V |
| 30 | M | R | 14 | 16 | 5 | LEV, CBZ, LCM | L anterior temporal signal abnormality | CD | Yes | 18 | V |
| 52 | M | R | 46 | 6 | 60 | PHT, LMG | L MTS + anterior temporal CD | HS | Yes | 25 | V |
| 21 | F | L | 15 | 6 | 2 | OXC, LCM | L anterior temporal encephalocele | Gliosis | Yes | 22 | Normal |
| 36 | F | R | 32 | 4 | 1 | LEV, LTG, TPM | L hipp CD | Insuff. sample | Yes | 12 | V |
| 63 | F | R | 31 | 32 | 3 | LCM, ZNS | L anterior temporal cavernous malformation | Cavernous malformation | Yes | 18 | NV |
| *Patients with right TLE* | | | | | | | | | | | |
| 34 | M | R | 15 | 19 | 2 | LTG | R MTS | Gliosis | Yes | 20 | NV |
| 34 | F | R | 14 | 20 | 60 | LEV, LTG | R temporal hyperintensity | Gliosis | No | 20 | NV |
| 52 | M | R | 47 | 5 | 1 | LEV | R temporal CD | CD | No | 17 | NV > V |
| 53 | F | R | 45 | 8 | 6 | OXC | Normal | Mild cortical disorganization | Yes | 18 | NV > V |
| 43 | M | R | 41 | 2 | 1 | LEV, LTG | Normal | – | No surg. | NA | |
| 45 | F | R | 36 | 9 | 2 | VPA, LCM | Hipp malformation | Gliosis | Yes | 7 | NA (non-English speaking) |
| 40 | M | R | 20 | 20 | 3 | VPA, LCM | R amygdala hypertrophy | Insuff. sample | Yes | 32 | NV > V |
| 39 | M | R | 8 | 31 | 2 | LTG, LEV | R MTS | Gliosis | Yes | 25 | Normal |
| 20 | M | R | 1 | 19 | 2 | OXC, LCM | Bilateral hipp atrophy | Gliosis | No | 3 | NV |
| 47 | M | R | 10 | 37 | 2 | VPA, LEV | R MTS | HS | Yes | 23 | NV |
| 37 | M | R | 4 | 33 | 3 | TPM, LTG, LEV, CBZ | R MTS | HS, CD | Yes | 12 | NV |

CBZ—carbamazepine, CD—cortical dysplasia, hipp—hippocampal, L—left, LEV—levetiracetam, LTG—lamotrigine, MTS—mesial temporal sclerosis, NV—nonverbal, OXC—oxcarbazepine, PGB—pregabalin, PHT—phenytoin, R—right, SF—seizure-free (without surgery), Sz—seizure, VPA—valproate, and V—verbal.

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